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08/249,689	05/26/1994	PAUL R. SCHIMMEL	MIT5261	9517

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EXAMINER	
BRUSCA, JOHN S	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.

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EXAMINER	
ART UNIT	PAPER
	74

DATE MAILED:

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Commissioner for Patents

The Examiner has requested the Board of Patent Appeals and Interferences for a rehearing of the panel decision entered in Appeal No. 2003-1335 (Paper No. 70, mailed October 30, 2003). A copy of the request is attached for appellants' consideration.
A non-extendable ONE MONTH time period is set from the date of this communication for appellants to respond.

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS

To: Gary V. Harkcom, Acting Chief Administrative Patent Judge

From: Jasemine C. Chambers and Bruce Kisliuk

Directors, Technology Center 1600

Via Stephen G. Kunin

Deputy Commissioner for Patent Examination Policy

Date: October 3, 2004

Re: Request for reconsideration of the decision by the Board of Patent Appeals and Interferences reversing the rejections of certain claims in Application Serial No. 08/249,689

Background

Prosecution history

Application No. 08/249689, filed on 26 May 1994, is a continuation of Application No. 08/129787, filed 29 September 1993, now abandoned, which is a continuation of Application No. 07/586534, filed 21 September 1990, now abandoned. In Application No. 08/249689 an Examiner's Answer was written by John S. Brusca, then of Art Unit 1805, on 22 January 1997 maintaining a rejection of all claims under 35 U.S.C. § 112, first paragraph for lack of enablement. The Board of Appeal and Interferences reversed the rejection on 30 April 2001 and raised a new grounds of rejection under 35 U.S.C. § 112, first paragraph for lack of written description for all product claims. A second Examiner's Answer maintaining the rejection for lack of written description for all product claims was written by John S. Brusca, now of Art Unit 1631, on 02 January 2003. The Board of Appeals and Interferences reversed the rejection for product claims limited to a tRNA target on 30 October 2003.

This memo requests reconsideration of the Board's decision reversing the rejection of product claims drawn to compounds that bind to a tRNA target.

Current status of the claims

Upon entry of the amendment following the decision of appeal (filed December 24, 2003), the status of the claims is as follows. Claims 1, 3-11, 13-16, and 18-21 are pending and allowed. Claims 1, 3-10, 14-16, and 20 are drawn to methods of designing compounds that bind to the minor groove and inhibit the function of tRNA molecules. Claims 11, 13, 18, 19, and 21 are drawn to compounds that bind to the minor groove and inhibit the function of tRNA. The compound claims 11, 13, 18, 19, and 21 are the sole subject of this memo.

Representative method claim

1. A method for designing a compound specifically inhibiting targeted ribonucleic acid function comprising the steps of:

(a) determining the nucleotide sequence in the targeted ribonucleic acid that is critical to function;

(b) determining the secondary structure of the region of the targeted ribonucleic acid in which the critical site is located;

(c) determining the three-dimensional structure of the targeted RNA, including the position of the critical site relative to the major and minor grooves;

(d) determining the sequence of nucleotides and structure flanking the critical site in the targeted ribonucleic acid that is specific to the critical region of the ribonucleic acid to be inhibited and within the minor groove; and

(e) synthesizing a compound that will bind specifically to the critical site within the minor groove of the targeted ribonucleic acid thereby inhibiting targeted ribonucleic acid function.

Representative compound claim

11. A complementary compound comprising hydrogen bond donor and acceptor sites arranged to specifically bind and inhibit the function of a targeted RNA molecule, wherein the compound is specifically directed to and binds to a critical region within the minor groove of the acceptor stem of a tRNA molecule, identified by a combination of the primary, secondary and tertiary structure of the critical region.

Summary

The Invention and Prosecution of the Application

Application 08/249689 describes the three dimensional structure of tRNA molecules, and discloses that the sequences of tRNA molecules are known. The specification shows on page 7 that sequence-specific discrimination by molecules that interact with helical regions of RNA occurs mainly in the shallow minor groove rather than in the deep and narrow major groove because the minor groove is more accessible to interacting molecules. The specification shows computer-mediated methods of designing molecules that fit shapes of target molecules. The specification does not show a working example of designing a compound that binds to the minor groove of any RNA molecule. The specification discusses naturally occurring biological molecules such as tRNA synthetases that apparently bind to the minor groove of tRNAs to facilitate the

normal function of tRNAs. The specification states that compounds that bind to the minor groove and inhibit the function of RNA molecules may be polypeptides, organic molecules, or nucleic acids.

The specification originally claimed **methods of designing** compounds that bind to the minor groove of the genus of all RNA molecules and inhibit the activity of the RNA molecules. The specification also originally claimed **compounds** that bind to the minor groove of the genus of all RNA molecules and inhibit the activity of the RNA molecules. In some embodiments the RNA was limited to tRNA, and the compounds were limited to nucleic acids.

All original claims were rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. Some claims were also rejected for double patenting. The rejections were appealed to the Board of Patent Appeals and Interferences. The Board maintained the double patenting rejections, which the applicants subsequently overcame by amendment and filing of a terminal disclaimer. The Board reversed the rejection for lack of enablement. The Board instituted a new grounds of rejection for all compound claims (but not the method claims) under 35 U.S.C. § 112, first paragraph for lack of written description. The rejection for lack of written description of the compound claims was maintained by the Office and the applicants appealed to the Board. The Board affirmed the rejection for lack of written description for those claims drawn to compounds that bind the minor groove and inhibit the function of **the genus of all RNA molecules**. The Board reversed the rejection for lack of written description for those claims drawn to compounds that bind the minor groove and inhibit the function of

tRNA molecules. The applicants subsequently filed an amendment that limits all compound claims to compounds that bind the minor groove and inhibit the function of tRNA molecules, in accordance with the Board decision.

Basis of the reversal by the Board of the rejection for lack of written description for the compound claims

The Board analogized the description of compounds that bind tRNA to that of description of antibodies that bind a described antigen. In support of the decision, the Board summarized the following passage from *Enzo Biochem Inc, v. Gen-Probe Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002):

It is not correct, however, that all functional descriptions of genetic material fail to meet the written description requirement. The PTO has issued Guidelines governing its internal practice for addressing that issue. The Guidelines, like the Manual of Patent Examining Procedure ("MPEP"), are not binding on this court, but may be given judicial notice to the extent they do not conflict with the statute. See Molins PLC v. Textron, Inc., 48 F.3d 1172, 1180 n.10, 33 USPQ2d 1823, 1828n.10 (Fed. Cir. 1995). In its Guidelines, the PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Guidelines, 66 Fed. Reg. at 1106 (emphasis added). For example, the PTO would find compliance with § 112, ¶ 1,

for a claim to an "isolated antibody capable of binding to antigen X," notwithstanding the functional definition of the antibody, in light of "the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature." Synopsis of Application of Written Description Guidelines, at 60, available at http://www.uspto.gov/web/patents/guides.htm ("Application of Guidelines").

The Board stated that because the structure of the target RNA is known, the claimed functional characteristics of the compounds (binding and inhibition of function) are coupled with a structure that is sufficiently known or disclosed. The Board also noted that the claimed compounds would possess hydrogen bond donor or acceptor sites that would have known spatial locations and orientations relative to the target tRNA. The Board distinguished claims limited to tRNA targets from those claims with generic RNA targets. The Board stated that the structure of compounds with generic RNA targets were not considered to be adequately described because of the lack of description of the structure of the genus of RNA target molecules.

Reasoning supporting a clear error by the Board of Patent Appeals and Interferences

The Board decision is inconsistent with the holding in *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 69 USPQ2d 1886 (Fed. Cir. 2004), which was decided on February 13, 2004 (subsequent to the date of the decision on appeal in the instant application). Furthermore, the Board made an incorrect

analogy between description of antibodies whose antigenic target is described and description of a compound whose binding target is described.

In *Univ. of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004), the CAFC ruled on a fact situation similar to the instant claims. The claims in the University of Rochester patent at issue (the '850 patent) directed to a method of inhibition of cyclooxygenase COX-2 were not supported by an adequate written description because the specification did not describe the structure of COX-2 inhibitors. The patent merely described the COX-2 target and methods of assaying for inhibitors. The CAFC held the patent invalid for lack of written description of the inhibitors used in the method. The CAFC stated:

[2] We agree with Pfizer that the '850 patent is deficient in failing to adequately describe the claimed invention. First, although compliance with the written description requirement is a question of fact, *Vas-Cath*, 935 F.2d at 1116, Rochester's argument that a patent may not be held invalid on its face is contrary to our case law. In *PIN/NIP, Inc. v. Platte Chemical Co.*, 304 F.3d 1235 [64 USPQ2d 1344] (Fed. Cir. 2002), for example, we held that a patent can be held invalid for failure to meet the written description requirement, based solely on the language of the patent specification. After all, it is in the patent specification where the written description requirement must be met. Similarly, in *TurboCare Division of Demag Delaval Turbomachinery Corp. v. General Electric Co.*, 264 F.3d 1111 [60 USPQ2d 1017] (Fed. Cir. 2001), we held that "[n]o reasonable juror could find that [an appellant's] original disclosure was sufficiently detailed to enable one of skill in the art to recognize that [the appellant] invented what is claimed," and accordingly upheld a grant of summary judgment. *Id.* at 1119.

Second, it is undisputed that the '850 patent does not disclose any compounds that can be used in its claimed methods. The claimed methods thus cannot be practiced based on the patent's specification, even considering the knowledge of one skilled in the art. No compounds that will perform the claimed method are disclosed, nor has any evidence been shown that such a compound was known. The '850 patent does contain substantial description of the cyclooxygenases, including the nucleotide sequences of coding and promoter regions of the genes that encode human COX-1 and COX-2 and a comparison of those sequences. *See, e.g.*, '850 patent, figs. 6A-6B, 10A-10D, and 11A-11C. The patent also describes in detail how to make cells that express either COX-1 or COX-2, but not both, *id.* §5.2, at cols. 8-20, as well as "assays for screening compounds, including peptides, polynucleotides, and small organic molecules to identify those that inhibit the expression or activity of the PGHS-2 gene product; and methods of treating diseases characterized by aberrant PGHS-2 activity using such compounds," *id.* at col. 8, ll. 2-7; *see also id.* §5.6, at cols. 24-25. Such assay methods are in fact

> claimed in the '479 patent, *i.e.*, Rochester's *other* patent based on the same disclosure. The '850 patent specification also describes what can be done with any compounds that may potentially be identified through those assays, including formulation into pharmaceuticals, routes of administration, estimation of effective dosage, and suitable dosage forms. *Id.* §5.8, at cols. 27-34. As pointed out by the district court, however, the '850 patent does not disclose just "*which* 'peptides, polynucleotides, and small organic molecules' have the desired characteristic of selectively inhibiting PGHS-2." *Univ. of Rochester*, 249 F. Supp. 2d at 224. Without such disclosure, the claimed methods cannot be said to have been described. As we held in *Lilly*, "[a]n adequate written description of a DNA ... 'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." 119 F.3d at 1566 (quoting *Fiers*, 984 F.2d at 1171). For reasons stated above, that requirement applies just as well to non-DNA (or RNA) chemical inventions.

Similarly, in the application at issue, the specification describes what can be done with compounds, such as peptides, organic compounds, and nucleic acids, which bind to a particular region of tRNA. However, the specification does not describe which compounds have the desired characteristics, beyond the fact that the compounds have hydrogen bond donor and acceptor sites. Attention is drawn to the following similarities between the application at issue (particularly claims 11, 13, 18, 19, and 21) and the patent at issue in the *Univ. of Rochester* case:

1) Structures of a binding target of a claimed chemical compound or its method of use are described.

2) Structures of a claimed compound or its method of use are not described, nor are correlations between the chemical compound and its function described.

3) Methods of screening or designing the chemical compound are described.

In holding that the claims of the patent at issue in *Univ. of Rochester v. G.D. Searle & Co.* lack an adequate written description, the Federal Circuit observed that claims drawn to compounds should be held to the same standards of written description as claims drawn to methods of using the compound. Given the close similarity between the facts at issue in the *Univ. of Rochester v. G.D. Searle & Co.* decision and instant claims 11, 13, 18, 19, and 21 (differing principally in the form of the claims and the specifics of

the hypothetical structures being claimed), the instant claimed invention lacks an adequate written description for the reasons set forth in the *Rochester* decision.

In addition, it is the examiner's position that the Board made an error in fact in determining that there is a direct correlation between description of antibodies whose antigenic target is described and description of a compound whose binding target is described. The Office has taken the position that description of an antigen generally is sufficient to describe an antibody that specifically binds the antigen. This is because one of skill in the art can make an antibody specific to an antigen by immunization of an animal with the antigen. The immunized animal will produce antibody molecules that differ from generally known structures of antibodies only in the binding site of the antibodies. Prior knowledge of the complete structure of the antibody molecule is not required because the antibody molecule can be readily obtained from the immunized animal. The CAFC has recently issued a decision in agreement with the position of the Office on this point in *Noelle v. Lederman*, 69 USPQ2d 1508 (Fed. Cir. 2004). Of central importance is the concept that a correlation between structure and function is required if functional language serves to adequately describe a product.

In contrast, the compound claims of Application No. 08/249689 are in part defined by claimed functions of binding and inhibition of target tRNA. The claims are drawn to a wide genus of compounds that the specification indicates may be polypeptides, organic molecules, or nucleic acids. Although the structure of the target tRNA is provided, one of skill in the art has no guidance as to the structures of the claimed compounds. Although the Board gave some weight to the fact that the claimed compounds form hydrogen bonds with the target tRNA, the description of the structures of the claimed compounds ends where the hydrogen

bond acceptors or donors of the claimed compounds begin. However, unlike methods of making antibodies, the art of making the claimed compounds is not well known and mature. At the time of filing, neither the prior art nor the specification showed working examples of the claimed compounds. The only method of making the claimed compounds detailed in the specification is by the experimental and computer modeling method of claim 1. Because the described method does not result in a predictable structure, and the claimed functions do not have a disclosed or well-known correlation to structure, the structures of the claimed compounds cannot be considered described. Description of the claimed compounds is not analogous to description of an antibody that specifically binds a described antigen because the structures of the claimed compounds are not predictable and the method of isolation of the claimed compounds involves experimentation without prior knowledge of the results.

In Trilateral Project B3b (Theme: Comparative study on "reach-through claims"), available at http://www.uspto.gov/web/tws/B3b_reachthrough.pdf, a hypothetical patent application was considered. In Case 1, the application disclosed the structure of a receptor protein and methods of isolation of agonists of the receptor, but did not describe the structure of agonist molecules that interact with the receptor. Case 1 claim 3 was drawn to an isolated and purified agonist of the described receptor. The USPTO comments regarding written description of claim 3 for Case 1 are as follows:

> The claimed invention is drawn to an agonist identified by the method of claim 2. However, no structural or specific functional characteristics of such an agonist are provided, nor is there any indication that the applicant has possession of any agonist. This situation is analogous to that of *Regents of the University of California v. Eli Lilly*, 119 F3d 1559, 43 USPQ2d 1398 (Fed, Cir. 1997). Because

one skilled in the art would conclude that the inventors were not in possession of the claimed invention, the claim fails to comply with the written description requirement.

In both Application 08/249689 and the hypothetical application of Trilateral Project B3b, compounds such as drugs are described only by the structure of the biological target to which they bind. Although in the hypothetical application the crystallographic structure of the receptor target was not described, the amino acid sequence of the receptor target was described. In Application 08/249689 the crystallographic structure of the target is available. However, generation of crystallographic structures is becoming routine in the art, and suitable bioassays allow for screening of compounds without knowledge of the crystallographic structure of the target. What is of key importance is not the extent of description of the structure of the target, but the extent of description of the compound that binds the target. It should also be noted that the hypothetical application disclosed methods of isolating an agonist. Application 08/249689 also describes and claims in claim 1 a method of isolating the claimed compounds. Although such methods were considered described in the hypothetical application, the products identified by the methods were not considered described. The product claims of Application No. 08/249689 are therefore analogous to the hypothetical agonist claims of Trilateral Project B3b.

Conclusion

Recent decisions of the Federal Circuit and guidance provided by the USPTO (in the form of the Trilateral Comparative Study referenced above) reinforce the conclusion that the product claims of Application 08/249689 are not adequately described. If such reach through

claims were allowed, then mere compilation of target molecule sequences would allow applicants to patent any later discovered drug that interacts with the target. We respectfully request reconsideration of the Board's decision in Application 08/249689 for the reasons set forth above.